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Running title: Preoperative Parecoxib and Preemptive Analgesia

Implication statement: Preoperative parecoxib does not provide clinically significant preemptive analgesia. However, perioperative parecoxib provides substantial postoperative

analgesia after total hip arthroplasty for the first 24 hours after surgery without increasing perioperative bleeding

Abstract

Background: Parecoxib, a selective cyclooxygenase-2 inhibitor, may reduce postoperative pain when administered before surgery without increasing bleeding.

Methods: We randomly assigned **62** patients scheduled for total hip arthroplasty to the following intravenous dosing schedule: 1) placebo at induction, at wound closure, and 12 hours after induction (control); 2) parecoxib 40 mg at induction, placebo at wound closure, and parecoxib 40 mg 12 hours after induction (pre); or, 3) placebo at induction, parecoxib 40 mg at wound closure, and parecoxib 40 mg 12 hours after induction (post). Pain scores at rest and with movement recorded every 4 hours for 24 hours using a visual analog scale. Treatment side effects were recorded every 4 hours. Red cell loss for 5 days after surgery was calculated.

Results: Postoperative pain scores were less in pre and post groups than in the control group. Postoperative bleeding was similar in the three groups. There were no significant differences between pre and post groups, nor was their any trend suggesting a pre-emptive analgesic efficacy from preincision administration of parecoxib. Morphine use in the Post Anesthesia Care Unit was reduced in the pre and post groups compared with the control group (14.2±2.0, and 15.7±2.0, versus 20.4±2.3 mg), although the trend was only significant ($p < 0.05$) in the pre group. The first pain score was also reduced in the pre and post groups compared to the control group (56.1±7.5 and 64.2 ± 7.0 versus 78.3±5), but this was also only significant for the pre group ($p=0.001$). The delay for first analgesic demand was increased for both the pre and post group compared to the control group (38±9 and 28.2 ± 6.6 versus 18±6 min), but again this was only significant for the pre group ($P=0.05$). Twenty-four hour consumption of morphine was similar in the pre (26±12 mg) and post groups (25±13 mg); both of which were significantly less than control group (47±27 mg, $P<0.001$).

Conclusions: Administration of parecoxib before hip arthroplasty did not provide preemptive analgesia. There was a trend towards improved analgesia immediately after surgery with preincision administration, consistent with the expected time course of NSAID drug effect. Perioperative parecoxib administration, consisting of two injections spaced 12 hours apart, improved postoperative analgesia over the first 24 hours without increasing bleeding.

Key words: anesthesia, analgesia, parecoxib, preemptive analgesia, coagulation, bleeding.

Introduction

Tissue injury and inflammation induce cyclooxygenase-2, both in the periphery and the central nervous system (1). Cyclooxygenase-2 is responsible for the synthesis of prostaglandins, which sensitize the nociceptor (2) and act as excitatory neuromediators in the central nervous system (2,3). In animal models, the inhibition of constitutive cyclooxygenase-2 and reduction of its inducible form reduce the peripheral and central sensitization that occurs after tissue injury (3,4). Additionally, rofecoxib limits both primary and secondary hyperalgesia in a human pain model (5). Therefore, we hypothesized that inhibition of cyclooxygenase-2 before tissue injury might enhance the analgesia provided by parecoxib for postoperative pain control.

Initial clinical studies of preemptive analgesia were negative (6), but a recent systematic review analyzed 66 studies related to 5 groups of interventions: epidural analgesia, peripheral local anesthetic infiltration, systemic N-Methyl-D-Aspartate receptor antagonists, systemic nonsteroidal antiinflammatory drugs (NSAIDs), and systemic opioids (7). The authors report a significant preemptive effect with epidural analgesia, local infiltration, and systemic NSAID administration. However, this review included only a single clinical study that examined a possible preemptive analgesic effect of a cyclooxygenase-2 inhibitor, and that for arthroscopic surgery (8).

The preoperative administration of NSAIDs may, therefore, offer improvement in the quality of postoperative pain management. However, the main limitation of perioperative use of nonselective NSAID is increased bleeding with an estimated incidence of 1% after major surgery (9). This risk of bleeding is even increased when nonselective NSAIDs are given before surgery (10,11). Therefore, despite data suggesting the possible preemptive effect of nonselective NSAIDs, the preoperative administration of these drugs is not presently part of postoperative pain control guidelines.

Parecoxib (Pfizer, Paris, France) is a selective inhibitor of cyclooxygenase-2 available for postoperative IV analgesia and a pro-drug, which is metabolized by the liver to valdecoxib. It is effective for postoperative pain control after various types of surgery (12,13). Preoperative administration of parecoxib also provides effective analgesia (14-17); however, no study has tested the preemptive analgesic effect of parecoxib in major surgery using recommended methodologies (18). We therefore conducted a prospective, randomized study to test the hypothesis that the preoperative administration of parecoxib for total hip arthroplasty provides better analgesia than postoperative administration, and that neither increases perioperative bleeding.

Methods

The local ethics committee (Comité Consultatif de Protection des Personnes pour le Recherche Biomédicale, Boulogne Billancourt, France) approved the study, and all patients gave written informed consent. We recruited 76 patients scheduled for total hip arthroplasty from two institutions (Hôpital Raymond Poincaré, Garches, and Hôpital Cochin, Paris, France)

The inclusion criteria included total hip arthroplasty under general anesthesia. Patients were excluded when they had contraindications to parecoxib, including cardiovascular pathology and renal insufficiency, previous hip surgery, hip trauma, or preoperative use of opioid or NSAID within 48 hours before surgery. Patients were withdrawn from the study if they 1) withdrew consent during the follow-up period; 2) developed a complication that required intervention within 24 hours after surgery; or, 3) required prolonged (> 60 minutes) mechanical ventilation after surgery.

Protocol

All patients were premedicated with hydroxyzine, 100 mg, before surgery. The same surgeon performed all total hip arthroplasties under a standardized anesthesia protocol combining propofol, sufentanil, a muscle relaxant, sevoflurane, and N_2O. Sufentanil was administered in bolus according to blood pressure and heart rate with a 0.15 mcg/kg sufentanil bolus in case of 15 % heart rate and/or 20% blood pressure increase compared with preoperative values. After surgery, postoperative pain was controlled by IV morphine given *via* a patient-controlled analgesia pump (PCA). No patient was given a peripheral nerve block, paracetamol or other NSAIDs.

Patients were randomly allocated to three groups: control, pre, and post. All patients received three IV injections: one with anesthesia induction, a second at wound closure, and a

third 12 hours after induction. All solutions were colorless and given in a volume of 2 mL, prepared **in the operating room** by an anesthesiologist not otherwise involved in the study. The control group received three placebo injections. The pre group received 40 mg parecoxib at induction, placebo for the second injection, and 40 mg parecoxib for the third injection. The post group received placebo for the first injection, 40 mg parecoxib for the second injection, and 40 mg parecoxib for the third injection. This study design was based on previous recommendations (18). A randomization list for each center, randomly assigned to groups based on computer-generated codes. The randomization instructions were stored in sequentially numbered opaque envelopes opened the day of surgery before induction of anesthesia.

Measurements

As soon as possible after arrival in the Post Anesthesia Care Unit (PACU), patients rated their pain on a 100-mm-long visual analog scale (VAS) (0 mm = no pain; 100 mm = worst imaginable pain). When the VAS pain score was more than 30 mm, IV morphine was titrated to effect. Patients could receive up to 3 mg of morphine, given every 5 minutes. Patients then used a PCA delivery system for IV morphine (1 mg bolus with a lockout time of 5 minutes). VAS pain scores at rest and movement (no standardized movement in the bed) were monitored every 4 hours for 24 hours after surgery by a nurse not aware of the patient allocation.

Morphine-related side effects were monitored every 4 hours for 24 hours after surgery. Sedation was quantified using a sedation score (0: no sedation; 1: patient intermittently sedated; 2: patient continuously sedated, but arousable with verbal stimuli; 3: patient continuously sedated, not arousable). Urinary retention was monitored with a score (0: no difficulties voiding; 1: difficulty voiding, no bladder catheterization; 2: bladder

catheterization). Nausea and vomiting were monitored using a score (0: no nausea or vomiting; 1: nausea or vomiting with no treatment; 2: nausea and vomiting requiring treatment). The duration of stay in the PACU was not monitored since the duration of stay after total hip arthroplasty in our institution is mainly related to blood transfusion rather than pain control.

The hematocrit (Hct) was determined on the day before surgery (D-1) and on day 5 after surgery (D5). The total numbers of autologous or homologous red blood cell concentrate (RBCC) transfusions were tabulated on Day 5. Blood loss was calculated as follows: the calculated blood loss corresponded to the sum of the uncompensated blood loss shown by the reduction in Hct and the blood loss compensated by transfusion. Uncompensated loss was calculated using the formula of Mercuriali and Inghilleri (19) and were expressed in mL of red blood cell volume (RBCV): uncompensated loss = (RBCV x Hct D-1) – (RBCV x Hct D5). The compensated loss corresponds to the sum of all the transfusions (autologous units and homologous units). For the calculations, we considered that RBCC have a Hct of 60%. The mean volume is about 250 mL, with 150 mL of pure RBC added to 100 mL of saline-adenine-glucose-mannitol. Therefore, in the calculation of the compensated loss, we considered that each RBCC compensates for 150 mL of blood with a Hct of 100%.

Statistical analysis

Previous results on the preemptive analgesic effect of NSAID (7) described a 48% reduction in supplemental analgesic consumption (range 0.31-0.65). According to previous results on morphine consumption after total hip arthroplasty in our institution (**mean ± SD; 43 ± 23**) (20), a total of 60 patients (20 in each group) was thus necessary to detect a 50% reduction in morphine use over 24 hours in the pre group compared with the post group with a type 1 error value of 0.05 and a type 2 error value of 0.10.

The main outcome was cumulative individual morphine consumption over the first 24 hours after surgery. Secondary outcomes were morphine titration in the PACU, morphine PCA use, VAS pain score in the PACU, time to first analgesic demand in the PACU, VAS pain score, morphine- and parecoxib-related side effects during the follow-up period, and total RBC loss over 5 days.

The morphine consumption and VAS pain scores were compared with ANOVA and Fisher's test. The frequency of dichotomous outcomes was compared with chi square test; $P < 0.05$ was considered statistically significant.

Results

Eleven patients were eliminated from the study: two patients withdrew consent, one required prolonged postoperative mechanical ventilation, two were inadvertently given paracetamol (one of the exclusion criterion), four because of inadequate order of treatment attribution (third injection made instead the second), one had a surgical complication that required intervention, and one because the patient's data were lost. Thus, data from 65 patients were analyzed for the PACU period (n=21 control group; n=22 pre group; n=22 post group). Two additional patients were eliminated from the study after morphine titration in the PACU: one patient withdrew consent and another was dropped because of lack of a third injection. **A last patient was eliminated after PACU due to one ketamine bolus administration in the PACU after the morphine titration. Thus, data from 62 patients were analyzed for morphine consumption over 24 hours and morphine-related side effects (n=21 control group; n=22 pre group; n=19 post group) and 63 patients for postoperative bleeding (n=21 control group; n=22 pre group; n=20 post group).**

Patient, surgery, and anesthesia characteristics were similar in the groups (Table 1).

Cumulative morphine consumption for the 24 hours after surgery (combined PCA use and PACU titration) was reduced by approximately 45% in both the pre and post group compared with the control group (Table 2). The average PCA morphine-sparing effect was 66% in the pre group and 72% in the post group compared with the control group (Table 2). The 4-hours intervals dose of IV PCA morphine was significantly reduced in the pre and post groups compared with the control group (Fig. 1).

Four of 22 patients in the pre group did not require morphine in the PACU whereas all those in the post group did and 1 of 21 in the control group did not (Table 2). The average reduction of morphine consumption for titration in the PACU was 32% in the pre group and 23% in the post group compared with the control group (Table 2, Figure 1).

The preoperative administration of parecoxib more than doubled the time to first analgesic demand in the PACU, but postoperative administration only increased it by 26%.

The first VAS pain score in the PACU before morphine titration was 29% less in the pre group than in the control group, but only 18% less in the post group than in the control group (Table 2, Figure 2). However, the pre and post scores were not significantly different (Figure 2).

Between 4 and 24 hours after surgery, VAS pain scores at rest and during movement were always lower in the pre and post groups than in the control group. However, this difference was statistically significant only between 12 and 24 hours after surgery (Figures 2 and 3). The incidence of analgesic-related complications was similar in all groups (Table 3). Bleeding and Hct five days after surgery were also comparable in each group (Table 3).

Discussion

The review by Ong et al. (7) and the accompanying editorial by Kissin (18) define preemptive analgesia as superiority of preoperative versus postoperative administration, and preventive analgesia as an effect persisting beyond the presence of the analgesic drug in the biophase. A preventive analgesic effect seems to be offered by drugs such as N-Methyl-D-Aspartate receptor antagonists like ketamine (21), while preemptive analgesia may be more specific to analgesic techniques like epidural anesthesia, peripheral local anesthetic infiltration, or systemic NSAIDs (7).

Authors comparing the preoperative administration of parecoxib to a placebo treatment found that preoperative parecoxib significantly reduced rescue analgesia over 24 hours (14,15,22,23). However, we did not observe a *preemptive* analgesic effect of parecoxib according to currently accepted criteria since preoperative administration of parecoxib had no significant impact on the amount of morphine consumed, pain scores, or time to first analgesic demand compared with postoperative administration.

Only one report has compared preoperative to postoperative administration of parecoxib and found a significant advantage to preoperative administration after general surgery (17). This study, though, was limited by a vague schedule of drug administration. Our results also contradict the recent meta-analysis (7) observing that the preoperative administration of NSAIDs offers a preemptive analgesic effect as reflected by a reduction in analgesic consumption and time to first analgesic demand. One explanation may be that all studies included in this meta-analysis, except for one using rofecoxib (8), referred to nonspecific NSAIDs (7). In fact, animal and clinical data suggest that inflammatory pain is not exclusively mediated by cyclooxygenase-2 induction (24,25). Cyclooxygenase-1 inhibition thus contributes to analgesia and may be necessary for a preemptive analgesic effect. Another plausible explanation may be that the limited power of our study was unable

to detect the preemptive analgesic effect reported in the meta analysis (7). Nonetheless, as seen by figures 1, 2, and 3, our study does not even show a hint of preemptive analgesic benefit in terms of sustained analgesic benefit beyond the initial benefit that can be explained by the slow onset of the dose given on wound closure in the post group. Thus, if there is preemptive analgesia with parecoxib, the benefit is modest at best.

In fact we added a post-hoc power analysis using the actual results. **The difference between the pre and post groups in terms of morphine consumption over 24 hours has a 95% confidence interval of (- 6.9 mg, 8.8 mg). Therefore, it seems to us that the largest detectable difference between the pre and post groups lies within bounds, which are not clinically important**.

Although we were unable to demonstrate preemptive or preventive analgesia, our results show that preoperative administration of parecoxib improved analgesia in the PACU. The time to first analgesic demand was doubled in patients given preoperative parecoxib, and the first postoperative pain score and amount of morphine for PACU titration were both reduced by one-third compared with the control group. However, we did not observe any impact on morphine-related side effects in the PACU and duration of stay in the PACU was mainly influenced by the need for blood transfusion.

The trend towards improved analgesia immediately after surgery following preincision administration of parecoxib, compared with parecoxib administered at wound closure, reflects the expected slow onset of NSAID analgesic effect (26). Parecoxib is a prodrug for valdecoxib, which is the active COX-2 selective moiety. Data from intramuscular administration of parecoxib demonstrate that the conversion to valdecoxib is rapid, and likely does not contribute to the delay in onset suggested by our data. (27). However, blood-brain equilibration could account for some of the delay, as suggested by the modest delay in CNS concentration seen with oral administration of valdecoxib (28).

In our study preoperative-administered parecoxib did not affect perioperative bleeding. Increased surgical site bleeding is a major problem with nonselective NSAIDs (9,11) and perioperative NSAID use increases bleeding with total hip arthroplasty (29,30). Experimental data have shown that valdecoxib does not interfere with platelet aggregation (31). Clinical studies have suggested that bleeding was not increased when rofecoxib (32) or valdecoxib (33) was given prior to major orthopedic surgery. Our study reaches similar conclusions, based on specific calculations of RBC loss. **The difference between the control and pre groups in terms of blood loss (RBC loss over 5 postoperative days) hours has a 95% confidence interval of (-15 ml, 190 ml) suggesting no clinically significant difference.** However, the study was not powered for blood loss comparisons and this may limit the meaning of this observation.

Cardiovascular toxicity has been responsible for the recent concerns about rofecoxib and resulted in new recommendations for the use of selective cyclooxygenase-2 inhibitors. Parecoxib is responsible for acute cardiovascular toxicity in the specific situation of cardiac surgery (34). Since the frequency of such toxicity is more related to prolonged use of cyclooxygenase-2 inhibitors or acute administration in a specific population at risk of cardiovascular complications, our study does not offer any additional information on this subject. Our study was not powered to identify cardiac complications, and none were observed.

In conclusion, parecoxib does not provide clinically significant preemptive analgesia. However, it improves postoperative analgesia, reduces the dose of morphine required by patients, and does not increase perioperative bleeding. The analgesic effects are still evident at 24 hours when two injections, spaced 12 hours apart, are given.

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Table 1: Patient, surgery and anesthesia characteristics.

	Control group	Pre group	Post group
Age (year)	63 ± 11	65 ± 9	62 ± 11
Sex (male / total)	12 / 21	12 / 22	10 / 22
Weight (kg)	76 ± 15	76 ± 13	73 ± 14
Duration of surgery (min)	118 ± 35	102 ± 27	108 ± 32
Cumulative perioperative sufentanil (µg)	58 ± 10	56 ± 7	57 ± 8
Preoperative hematocrit	0.43 ± 0.05	0.40 ± 0.04	0.42 ± 0.05
Hematocrit day 5 after surgery	0.32 ± 0.05	0.33 ± 0.04	0.33 ± 0.04

Values are expressed as mean ± SD.

PACU: Post Anesthesia Care Unit. Control group: patients received a placebo; pre group: patients received 40 mg intravenous parecoxib at induction of anesthesia and 12 hours after surgery; post group: patients received 40 mg IV parecoxib at wound closure and 12 hours after surgery.

Table 2 : Data on postoperative analgesia

	Control group	Pre group	Post group
Morphine consumption over 24 hours (mg)	47 ± 27	26 ± 12 ***	25 ± 13 ***
Cumulative morphine IVPCA (mg)	**26 ± 20**	**12 ± 9.1 *** **	**10 ± 14.7 *** **
Morphine titration in the PACU (mg)	**20.4 ± 10.5**	**14.2 ± 9.6 ***	**15.7 ± 8.9**
Patients who did not require morphine in the PACU (n)	1/21	4/20	0/22
Time to first analgesic demand (min)	18.0 ± 6.0	38.0 ± 9.0 *	28.2 ± 6.6
First VAS pain score in the PACU	78.3 ± 5	56.1 ± 7.5 *	64.2 ± 7.0

Value are expressed as mean ± SD

*** : $p < 0.001$; ** : $p=0.01$; * : $p < 0.05$ versus Control group

IVPCA: IV patient controlled analgesia; PACU: Post Anesthesia Care Unit. VAS: visual analog score

Control group: patients received a placebo; post group: patients received 40 mg IV parecoxib at wound closure and 12 hours after surgery; pre group: patients receiving 40 mg IV parecoxib at induction of anesthesia and 12 hours after surgery.

Table 3 : Incidence of side effects and bleeding.

	Control group	Pre group	Post group
Nausea or vomiting	5 (24%)	6 (30%)	6 (27%)
Sedation	7 (33%)	5 (25%)	4 (18%)
Urinary retention	5 (24%)	3 (15%)	2 (9%)
Bleeding (mL)	**516 ± 172**	**426 ± 168**	**428 ± 231**

Values are expressed as numbers (percentage) or mean ± SD.

Control group: patients received a placebo; pre group: patients received 40 mg IV parecoxib at induction of anesthesia and 12 hours after surgery; post group: patients received 40 mg IV parecoxib at wound closure and 12 hours after surgery.

No patient had severe sedation (sedation score = 3). No patient required bladder catheterization. The incidence of moderate sedation (sedation score = 1 or 2), moderate bladder dysfunction (urinary retention score = 1), and nausea and vomiting (nausea and vomiting score = 1 or 2) was similar in all groups.

Bleeding: calculated blood loss corresponding to the sum of the uncompensated blood loss shown by the reduction in hematocrit and the blood loss compensated by transfusion

Figure 1. Intravenous morphine use for 24 hours after surgery

Control group: patients received placebo; pre group: patients received 40 mg IV parecoxib at induction of anesthesia and 12 hours after surgery; post group: patients received 40 mg intravenous parecoxib at wound closure and 12 hours after surgery; PACU: Post Anesthesia Care Unit. Values are expressed as means ± SEMs. #$P < 0.05$ pre versus control group; ##$P = 0.002$ pre versus control group **$P = 0.008$ post versus control group

Figure 2. Visual analog pain scale scores at rest for 24 hours after surgery

Control group: patients received placebo; pre group: patients received 40 mg IV parecoxib at induction of anesthesia and 12 hours after surgery; post group: patients received 40 mg IV parecoxib at wound closure and 12 hours after surgery; PACU: Post Anesthesia Care Unit; VAS: visual analog pain score. Values are expressed as means ± SEMs. #$P = 0.02$ pre group versus control group; **$P = 0.01$ post group versus control group

Figure 3. Visual analog pain scale score on movement for 24 hours after surgery

Control group: patients received a placebo; pre group: patients received 40 mg IV parecoxib at induction of anesthesia and 12 hours after surgery; post group: patients received 40 mg IV parecoxib at wound closure and 12 hours after surgery; PACU: Post Anesthesia Care Unit; VAS: visual analog pain score. Values are expressed as means ± SEMs. #$P = 0.02$ pre group versus control group; **$P = 0.01$ post group versus control group

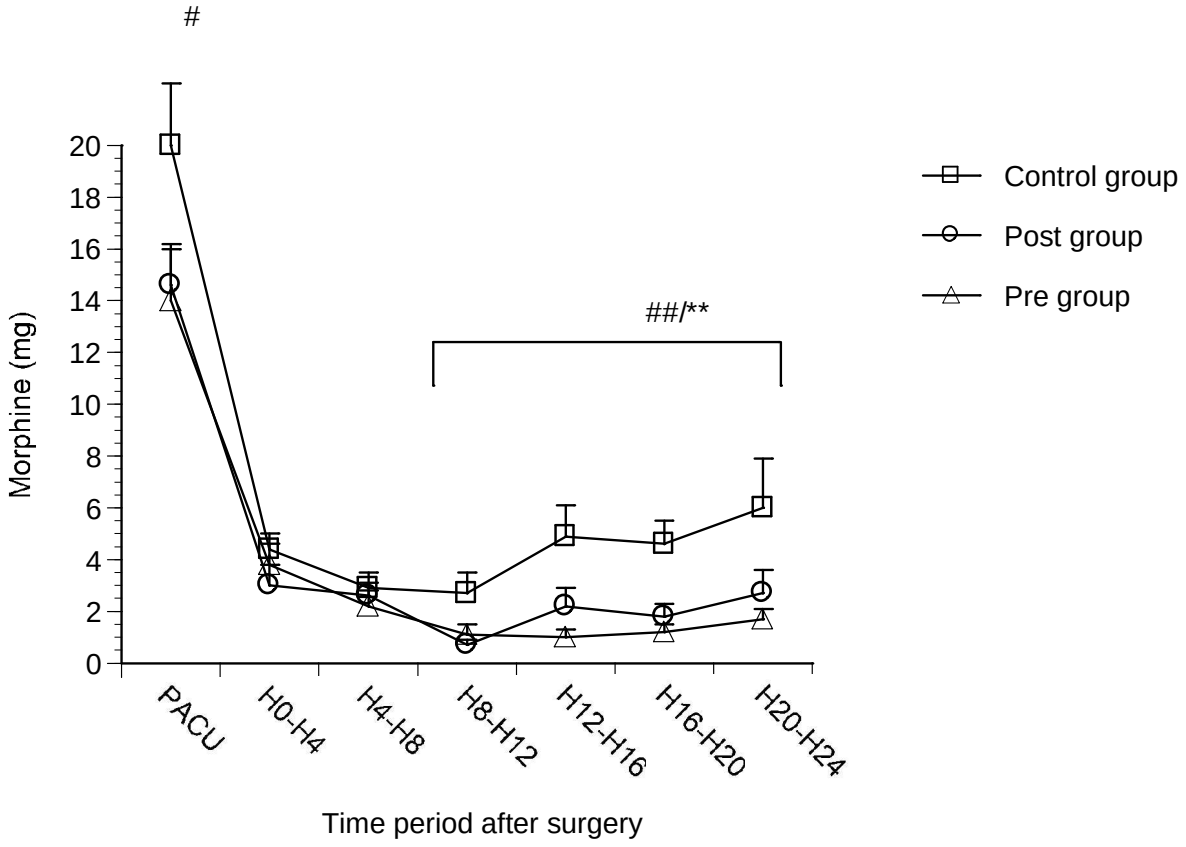
Figure 4. Calculated blood loss

This figure represents the calculated blood loss in the three groups

Control group: patients received a placebo; pre group: patients received 40 mg IV parecoxib at induction of anesthesia and 12 hours after surgery; post group: patients received 40 mg IV parecoxib at wound closure and 12 hours after surgery

The lowest, second lowest, middle, second highest and highest box point represent the 10^{th} percentile, 25^{th} percentile, median, 75^{th} percentile, 90^{th} percentile and median respectively. Means are represented by symbols. No statistical difference between the three groups

Figure 1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##/**
Morphine (mg)
0
2
4
6
8
10
12
14
16
18
20
PACU
H0-H4
H4-H8
H8-H12
H12-H16
H16-H20
H20-H24
Time period after surgery
Control group
Post group
Pre group

Figure 2

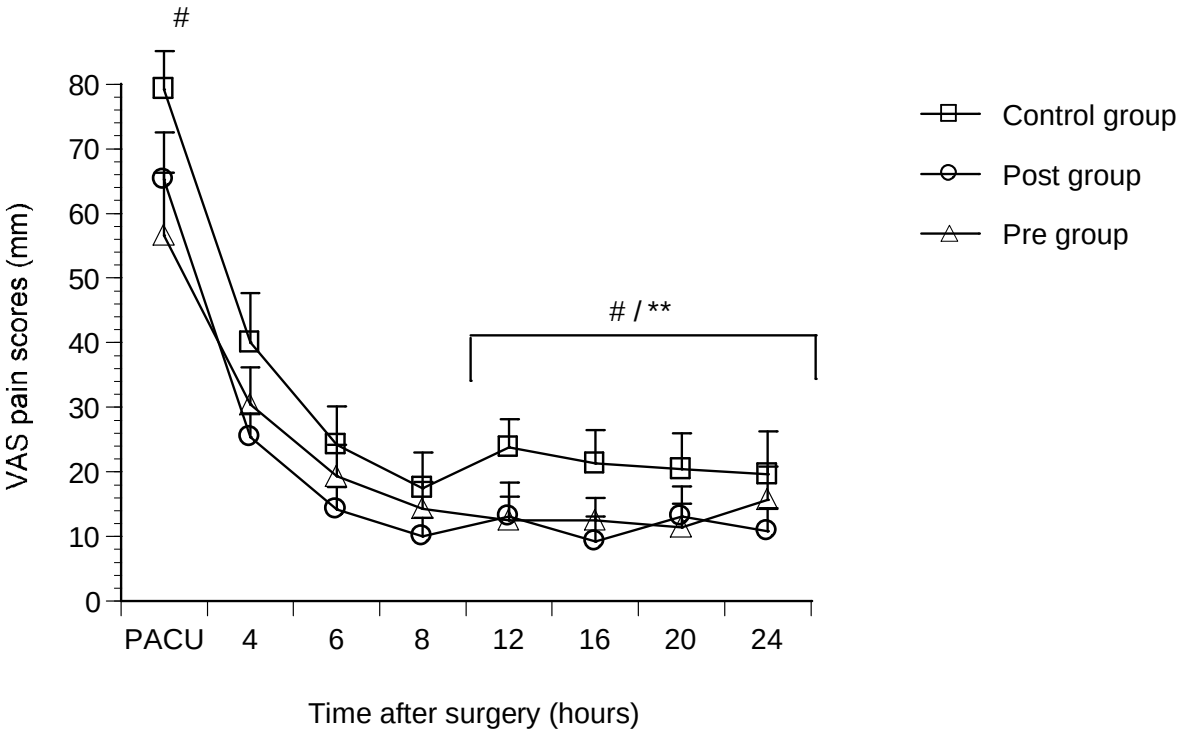

#
/ **
VAS pain scores (mm)
0
10
20
30
40
50
60
70
80
PACU
4
6
8
12
16
20
24
Time after surgery (hours)
Control group
Post group
Pre group

Figure 3

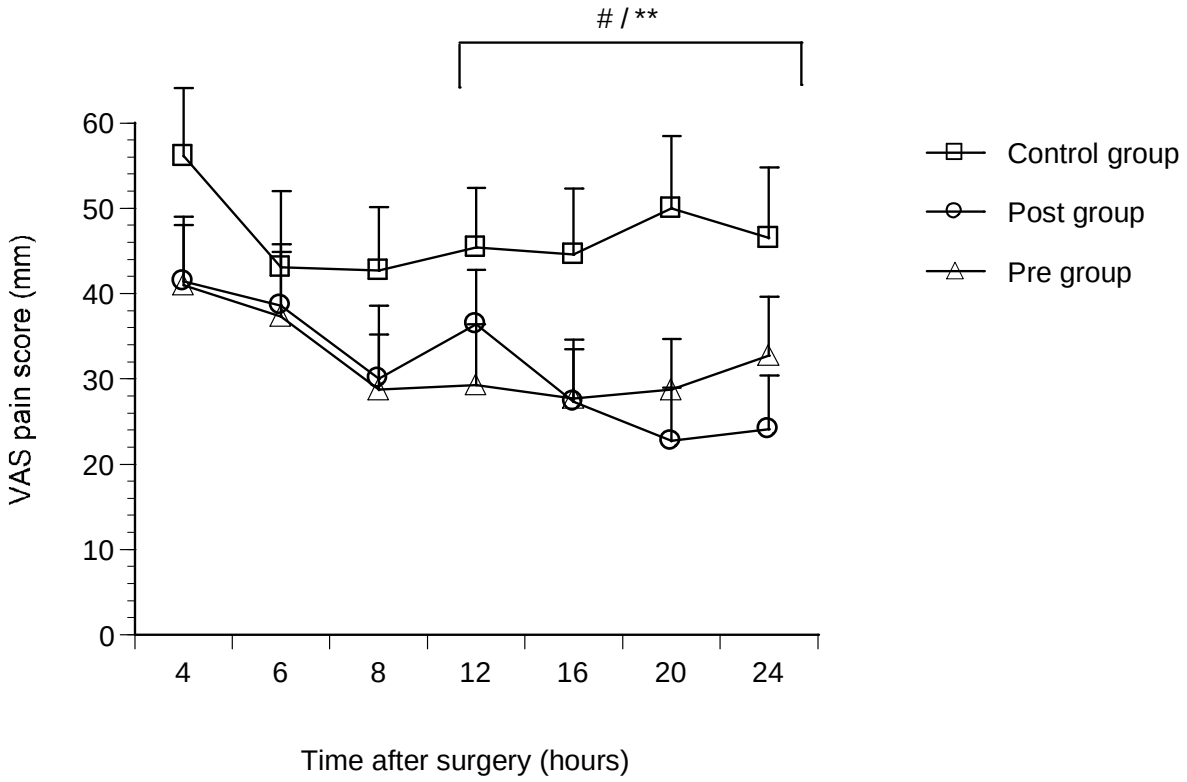
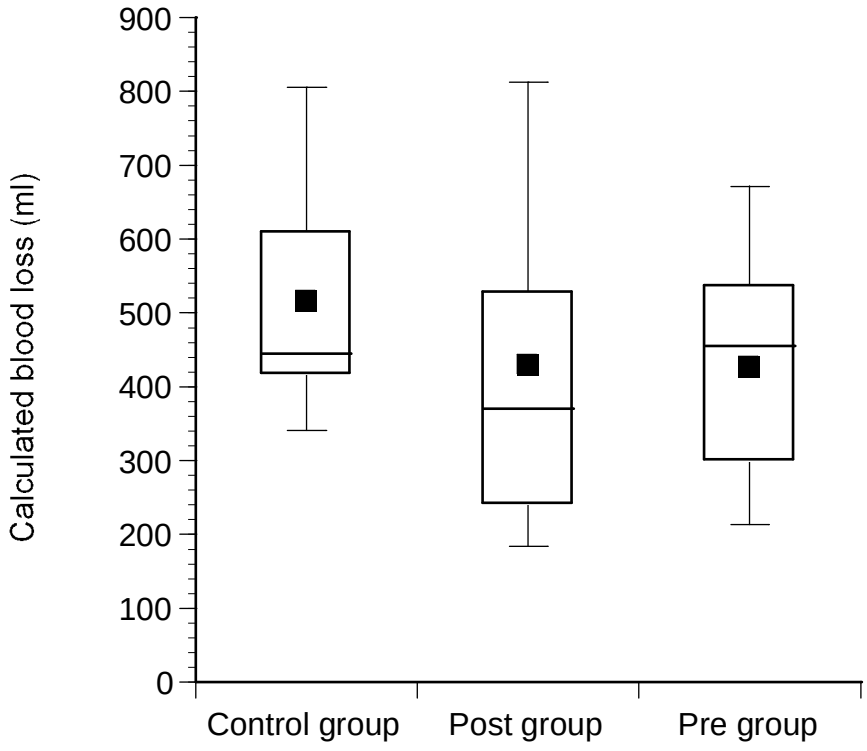

/ **
VAS pain score (mm)
0
10
20
30
40
50
60
4
6
8
12
16
20
24
Time after surgery (hours)
Control group
Post group
Pre group

Figure 4


900
800
700
600
500
400
300
200
100
0
Calculated blood loss (ml)
Control group
Post group
Pre group